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Microwave-assisted one-pot U-4CR and intramolecular O-alkylation toward heterocyclic scaffolds☆

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Abstract—The one-pot U-4CR and intramolecular O-alkylation sequence starting from 2-aminophenols in combination with α-bromoalkanoic acids, aldehydes, and isocyanides under controlled microwave heating has been established for a rapid access to highly functionalized 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines. With appropriate substitutions on the 1,4-benzoxazines, a microwave-assisted Cu-catalyzed intramolecular amidation was performed to furnish a novel class of heterocyclic conjugates of 1,4-benzoxazines with a 2-oxindole linked through a C–N single bond.

1. Introduction

Multicomponent reactions (MCRs)[1–3] are referred to as the one-pot processes, where multiple bonds are formed among three or more starting materials to furnish the product with essentially all of the atoms of the reactants. As a special subclass, the isocyanide-based MCRs (IMCRs)[3] offer a number of advantages originating from the unique reactivity of an isocyanide, which acts as a nucleophile and an electrophile at the same time. The most popular IMCRs are the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR), which produce linear α-acyloxycarboxamides and the peptide-like α-acylaminoamides, respectively.[3a] In recent years, a number of bifunctional components, such as oxo acids, amino acids, amino aldehydes, and isocyanoacetamides,[4] have been used for the synthesis of drug-like cyclic scaffolds.[3f] Various strategies for post-U-4CR modifications have been developed,[1a,3] including Armstrong's work on convertible isocyanides,[5] Hulme's UDC (Ugi/De-Boc/Cyclize) methodology,[6] and the combinations of U-4CRs with Wittig,[7] Heck,[8] RCM,[9] IMDA,[10] S_N2,[11] S_NAr,[12] and so on.[1a,3f] In Hulme's synthesis of benzimidazoles[6d] and quinoxalines[6e] via UDC, mono-*N*-Boc-protected phenylene diamines were used as the amine components. We envisaged that 2-aminophenols **1** could be used in U-4CRs as the amine component without protection of the phenolic hydroxyl group.[13] Therefore, a subsequent cyclization of **5a** or **5b** via a base-mediated O-alkylation or O-arylation (paths *a* and *b*) could be assumed (Chart 1). We report here our original results on the syntheses of heterocyclic scaffolds **6** via microwave-assisted one-pot U-4CR and intramolecular O-alkylation sequence. A further post-modification on **6** possessing R^2=*O*-BrC_6H_4 through the Cu-catalyzed intramolecular amidation (path *c*) has been successfully explored, providing a novel class of heterocyclic conjugates **8** linked through a C–N single bond.

2. Results and discussion

2-Aminophenols are commercially available and inexpensive building blocks and have been used in the syntheses of indoles,[14] benzofurans,[15] and 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines[16] in our previous studies. To the best of our knowledge, the parent 2-aminophenol was used in one example of U-4CR in combination with 4-fluoro-3-nitrobenzoic acid and the resultant adduct was subjected to a base-mediated intramolecular S_NAr reaction to furnish a 2-nitrobenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one in 25% isolated yield.[12a] We examined the U-4CRs by using five substituted 2-aminophenols (**1**), five aromatic aldehydes (**9**), two α-bromoalkanoic acids (**10**), and two isocyanides (**11**) at both room temperature and under controlled microwave heating,[17,18] respectively. The structures and yields of the

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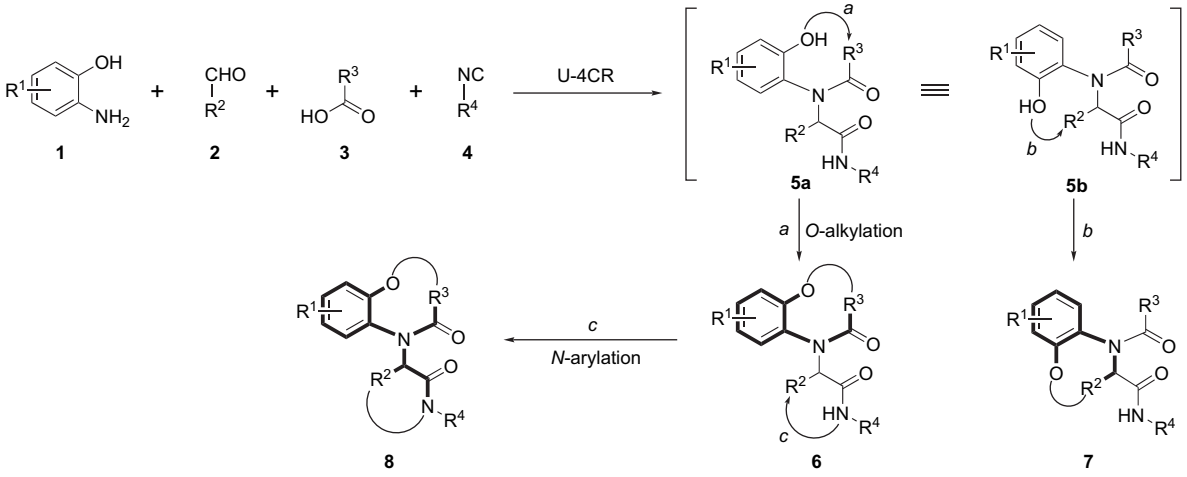
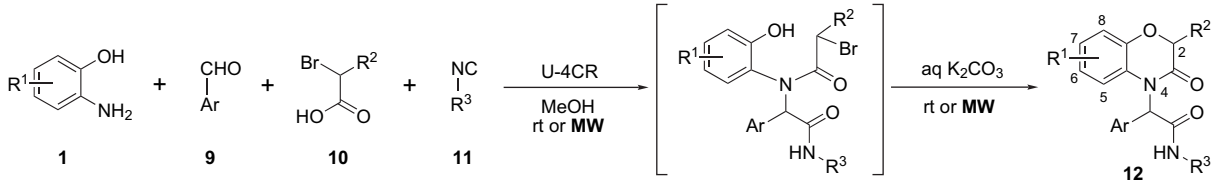


Chart 1. One-pot U-4CR-intramolecular O-alkylation and intramolecular amidation sequence toward heterocyclic scaffolds **6**–**8**.

products are summarized in Table 1. The U-4CR was carried out in MeOH and then, without isolation of the acyclic product, an aqueous solution of K_2CO_3 was added for promoting the intramolecular O-alkylation. A collection of 14 highly functionalized 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **12a**–**n** were isolated in 61–95% yields for the two-step reactions carried out at room temperature. Initially, the base-promoted cyclization was stirred at room temperature for overnight (8–12 h) (Table 1, entries 1–11). We found that the cyclization could complete in 20–45 min (Table 1, entries 12–14). Moreover, a prolonged reaction time generally improved the yield of U-4CR. It is not rare that some U-4CRs took up to 7 days at room temperature as in the cases of entries 12 and 13 of Table 1.

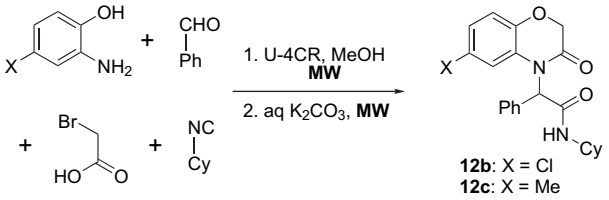
Table 1. One-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **12** via U-4CR and intramolecular O-alkylation[a]



Entry	**1** (R^1)[b]	**9** (Ar)	**10** (R^2)	**11** (R^3)	Room temp	MW[f]
					t_U (h),[c] t_A (h);[d] **12** (%)[e]	**12** (%)[e]
1	H	Ph	H	Cy	36, 11; **12a**: 79	81 (83)[g]
2	6-Cl	Ph	H	Cy	30, 11; **12b**: 75	82
3	6-Me	Ph	H	Cy	29, 12; **12c**: 85	85
4	6,7-$(CH_2)_4$–	Ph	H	Cy	36, 12; **12d**: 65	63
5	H	4-$MeOC_6H_4$	H	Cy	36, 12; **12e**: 77	72
6	H	Ph	Me	Cy	37, 12; **12f**: 65[h]	88[h]
7	H	2-Furyl	H	Cy	36, 12; **12g**: 61	56
8	H	2-FC_6H_4	H	Cy	37, 9; **12h**: 95	90
9	H	Ph	H	Bn	23, 8; **12i**: 90	83
10	6-Me	Ph	Me	Bn	24, 12; **12j**: 78[h]	84[h]
11	H	2-FC_6H_4	H	Bn	25, 12; **12k**: 79	81
12	7-Me	2-BrC_6H_4	H	Bn	168, 0.33; **12l**: 86	63
13	6-Me	2-BrC_6H_4	H	Bn	168, 0.33; **12m**: 84	64
14	6-Cl	2-BrC_6H_4	H	Bn	48, 0.75; **12n**: 73	52[i]

[a] An equal molar ratio of the four reagents was used with MeOH as the solvent.
[b] The numbering system of 1,4-benzoxazine is used.
[c] The reaction time for U-4CR at room temperature. A longer reaction time usually gave a higher yield.
[d] The reaction time for base-promoted cyclization at room temperature. In most cases, the reaction mixture was stirred for overnight. The cyclization should complete within 20–45 min as seen in entries 12–14.
[e] Isolated overall yields of **12** for the one-pot synthesis.
[f] All microwave-heated reactions were carried out in MeOH in closed pressurized vials with the reaction temperature measured by an IR sensor. For U-4CR step, the reaction mixture was heated at 80 °C for 20 min. After the addition of 1.2 equiv of aqueous K_2CO_3, the same vial was heated at 120 °C for 15 min for cyclization.
[g] The yield in the parentheses was obtained from the same reaction mixture heated in an oil bath instead of microwave irradiation.
[h] A ca. 60:40 mixture of diastereomers was obtained.
[i] Heated for 20 min for O-alkylation.

Table 2. Optimization of microwave-assisted one-pot synthesis of **12**[a]

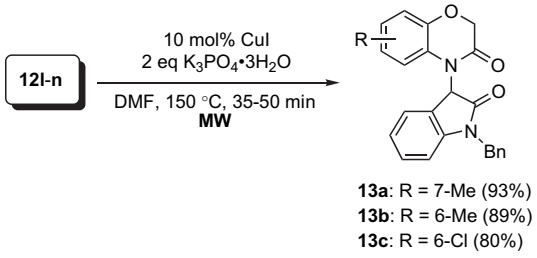


Entry	U-4CR T (°C); t (min)	K_2CO_3 (equiv)	O-Alkylation T (°C); t (min)	Yield (%)[b]
1	100; 20	2.0	150; 15	**12c**: 70
2	80; 20	1.2	120; 15	**12c**: 85
3	80; 20	2.0	150; 15	Black
4	80; 20	2.0	120; 15	**12b**: 71
5	80; 25	2.0	120; 15	**12b**: 64
6	80; 20	1.2	150; 15	**12b**: 64
7	80; 20	1.2	120; 15	**12b**: 82

[a] An equal molar ratio of the four reagents was used with MeOH as the solvent. The same microwave reaction as described in Table 1 was used.
[b] Isolated yield.

We attempted to accelerate the one-pot U-4CR and intramolecular O-alkylation for a high-throughput synthesis of **12** by using controlled microwave irradiation. With the purpose for an automated synthesis in mind, we optimized a set of unified reaction conditions by balancing between the reaction time and the product yield. Table 2 shows some results of the reactions under microwave irradiation, which were carried out in a closed vial, allowing heating above the boiling point of the solvent. We found that the U-4CR was not favorable at the temperature higher than 80 °C or with the reaction time longer than 20 min at 80 °C (entry 1 vs entry 2; entry 4 vs entry 5). Also, it was not advantageous to promote the O-alkylation at the temperature higher than 120 °C or with an excess base than 1.2 equiv (entry 3 vs entry 4; entry 6 vs entry 7; entry 4 vs entry 7). The optimized reaction conditions for the microwave-assisted one-pot process (entries 2 and 7 of Table 2) were then used for the one-pot synthesis of the 1,4-benzoxazines **12a–n** in 52–90% yields (Table 1). According to the data in Table 1, we can conclude that the product yields obtained from the microwave-assisted versions of the one-pot synthesis are generally comparable or slightly lower than the room temperature versions, except for several cases that produced the products **12l–n** in ca. 20% higher yields at room temperature (Table 1, entries 12–14). In terms of efficiency of the synthesis, the throughput is much higher for the microwave-assisted synthesis, i.e., 35 min (MW) versus 32–168 h (rt) for each compound. We also carried out the synthesis of **12a** by using a pre-heated oil bath and obtained the same result (Table 1, entry 1). Nevertheless, with the dedicated technical microwave reactor, it is much more easy to set and control the reaction temperature and to design and perform automated sequential synthesis of compound libraries.

For exploration of further annulation within **6** via the path *c* as depicted in Chart 1, we turned our attention to intramolecular amidation (N-arylation) of **12l–n** (Scheme 1). The CuI-catalyzed arylation of amines and amides has received growing interest in recent years.[19] We used controlled microwave heating for the intramolecular amidation[20,21] of **12l–n** in the presence of 10 mol % CuI and 2 equiv of $K_3PO_4 \cdot 3H_2O$ in DMF at 150 °C for 35–50 min. The



Scheme 1. CuI-catalyzed amidation under microwave heating.

expected 2-oxindoles **13a–c** were obtained in 80–93% yields. The structures of **13** represent a novel class of heterocyclic scaffold that features the conjugate of 1,4-benzoxazines with a 2-oxindole linked through a C–N bond. The ^1H and ^{13}C NMR spectra of **13** exhibit two sets of discrete signals (see Supplementary data), suggesting for atropisomers in solution. We performed HPLC analysis of **13a** over a chiral stationary phase and observed a dynamic

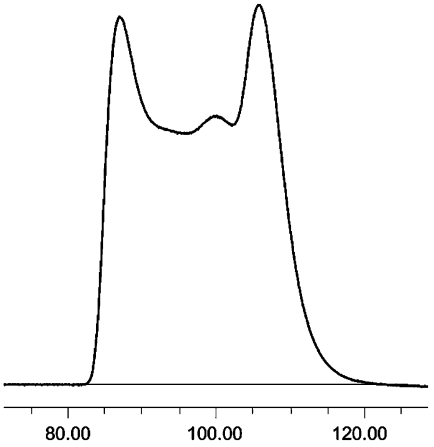


Figure 1. Dynamic HPLC chromatogram of **13a** (HPLC setting: Chiralcel OJ eluted with 90:10 hexane–*i*-PrOH at 10 mL/min and by UV detection at 254 nm). There are four diastereomers for **13a** arising from one stereogenic center and one stereogenic axis. Three out of four diastereomers are resolved.

HPLC chromatogram (Fig. 1). The latter is characteristic to atropisomerism of the C–N bond linked conjugates.

3. Conclusion

We have established a general and high-throughput synthesis of highly functionalized 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **12** starting from the building blocks, 2-aminophenols (**1**), aromatic aldehydes (**9**), α-bromoalkanoic acids (**10**), and isocyanides (**11**) via microwave-assisted one-pot U-4CR and intramolecular O-alkylation. Further post-modification has been showcased by the microwave-assisted CuI-catalyzed intramolecular amidation within **12l–n** to furnish a novel heterocyclic scaffold **13a–c**, which exhibits atropisomerism through rotation across the C–N single bond.

4. Experimental

4.1. General information and the microwave reactor

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (400 MHz for ^{1}H and 100 or 125 MHz for ^{13}C, respectively) with $CHCl_3$ or DMSO as the internal reference. IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the +ESI method. Melting points are uncorrected. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Methanol was distilled from magnesium before use. Reagents were obtained commercially and used as received. All microwave-assisted reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature.

4.2. General procedure for one-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines 12a–n at room temperature

To a 25-mL round bottom flask were added 2-aminophenol **1** (0.25 mmol), aldehyde **9** (0.25 mmol), and MeOH (2 mL), and the mixture was stirred for 15–30 min at room temperature. α-Bromoalkanoic acid **10** (0.25 mmol) was added to the mixture followed by stirring for another 5 min. Finally, isocyanide **11** (0.25 mmol) was added. After the resultant mixture was stirred at room temperature for 23–168 h, solid K_2CO_3 (52 mg, 0.38 mmol) was added. After the resultant mixture was stirred at room temperature for overnight (8–12 h for entries 1–11, Table 1) or 20–45 min (for entries 12–14, Table 1), the reaction mixture was quenched by water and the organic layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with EtOAc and petroleum ether (60–90 °C) to afford **12a–n**. The structures and yields of the products **12a–n** are given in Table 1.

4.3. General procedure for microwave-assisted one-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines 12a–n

To a 10-mL pressurized process vial were added 0.25 mmol each of 2-aminophenol **1**, aldehyde **9**, α-bromoalkanoic acid **10**, and isocyanide **11**, and MeOH (2 mL). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity and heated at 80 °C for 20 min. Then, an aqueous solution of K_2CO_3 (1 mL, 0.30 mmol) was added to the reaction vial through a syringe followed by heating at 120 °C for 15 min in the microwave cavity. Water was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with EtOAc and petroleum ether (60–90 °C) to afford **12a–n**. The structures and yields of the products are given in Table 1.

4.3.1. *N*-Cyclohexyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12a). A white crystalline solid; mp 140–142 °C; IR (KBr) 1684, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.37 (m, 5H), 7.12 (d, *J*=8.0 Hz, 1H), 7.07–7.00 (m, 2H), 6.94–6.90 (m, 1H), 6.19 (s, 1H), 6.12 (br d, *J*=8.0 Hz, 1H), 4.78 and 4.69 (ABq, *J*=15.2 Hz, 2H), 3.95–3.85 (m, 1H), 2.01–1.98 (m, 1H), 1.87–1.84 (m, 1H), 1.75–1.61 (m, 3H), 1.47–1.33 (m, 2H), 1.30–1.05 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.4, 146.0, 134.0, 128.8 (×2), 128.6, 128.2, 127.8 (×2), 124.4, 122.7, 117.6, 117.0, 68.2, 61.4, 48.6, 32.6, 32.5, 25.4, 24.5 (×2); MS (+ESI) *m*/*z* 403 (M+K$^+$, 100), 387 (M+Na$^+$, 26). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.51; H, 6.58; N, 7.84.

4.3.2. *N*-Cyclohexyl-2-(6-chloro-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12b). A white crystalline solid; mp 181–183 °C; IR (KBr) 1691, 1651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 5H), 7.05 (s, 1H), 6.89 (d, *J*=0.4 Hz, 2H), 6.05 (s, 1H), 5.95 (br d, *J*=8.0 Hz, 1H), 4.69 and 4.59 (ABq, *J*=15.2 Hz, 2H), 3.90–3.75 (m, 1H), 1.96–1.92 (m, 1H), 1.84–1.81 (m, 1H), 1.70–1.50 (m, 3H), 1.40–1.23 (m, 2H), 1.20–1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.9, 144.6, 133.6, 129.6, 129.1 (×2), 128.6, 127.9 (×2), 1276, 124.1, 117.9, 117.7, 68.1, 61.6, 48.7, 32.6, 32.5, 25.3, 24.5 (×2); MS (+ESI) *m*/*z* 439 (M+2+K$^+$, 33), 437 (M+K$^+$, 100), 423 (M+2+Na$^+$, 10), 421 (M+Na$^+$, 31). Anal. Calcd for $C_{22}H_{23}ClN_2O_3$: C, 66.24; H, 5.81; N, 7.02. Found: C, 66.26; H, 5.83; N, 7.09.

4.3.3. *N*-Cyclohexyl-2-(3,4-dihydro-6-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12c). A white crystalline solid; mp 148–150 °C; IR (KBr) 1686, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.85 (d, *J*=8.0 Hz, 1H), 6.83 (s, 1H), 6.72 (d, *J*=8.8 Hz, 1H), 6.09 (br d, *J*=8.0 Hz, 1H), 6.04 (s, 1H), 4.61 and 4.55 (ABq, *J*=15.2 Hz, 2H), 3.85–3.75 (m, 1H), 2.13 (s, 3H), 1.90–1.86 (m, 1H), 1.79–1.76 (m, 1H), 1.65–1.47 (m, 3H), 1.33–1.20 (m, 2H), 1.15–0.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.5, 143.8, 134.2, 132.4, 128.8 (×2), 128.6, 128.2, 127.7 (×2), 124.9, 117.9,

116.7, 68.3, 61.8, 48.6, 32.6, 32.4, 25.4, 24.5, 24.5, 20.9; MS (+ESI) *m/z* 401 (M+Na$^+$, 100). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.06; H, 7.07; N, 7.46.

4.3.4. *N*-Cyclohexyl-2-{3,4,6,7,8,9-hexahydro-3-oxo-2*H*-naphtho[2,3-*b*][1,4]oxazin-4-yl}-2-phenylacetamide (12d). A white crystalline solid; mp 138–140 °C; IR (KBr) 1686, 1656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5H), 6.78 (s, 1H), 6.76 (s, 1H), 6.16 (br d, J=8.0 Hz, 1H), 6.08 (s, 1H), 4.679 and 4.63 (ABq, J=15.2 Hz, 2H), 3.95–3.83 (m, 1H), 2.72–2.67 (m, 2H), 2.60 (br s, 2H), 2.00–1.90 (m, 1H), 1.90–1.88 (m, 1H), 1.80–1.57 (m, 7H), 1.45–1.31 (m, 2H), 1.25–1.08 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.4, 143.6, 134.2, 133.5, 131.5, 128.8 (×2), 128.1, 127.6 (×2), 126.5, 117.3, 116.9, 68.4, 62.0, 48.5, 32.5, 32.4, 28.9, 28.7, 25.4, 24.5, 24.5, 23.0, 22.8; MS (+ESI) *m/z* 457 (M+K$^+$, 41), 441 (M+Na$^+$, 100). Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69. Found: C, 74.53; H, 7.18; N, 6.66.

4.3.5. *N*-Cyclohexyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(4-methoxyphenyl)acetamide (12e). A white crystalline solid; mp 136–138 °C; IR (KBr) 1685, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.8 Hz, 2H), 7.05 (d, J=7.6 Hz, 1H), 7.01–6.94 (m, 2H), 6.88 (d, J=8.4 Hz, 3H), 6.02 (s, 1H), 5.97 (br d, J=7.6 Hz, 1H), 4.71 and 4.61 (ABq, J=15.2 Hz, 2H), 3.87–3.79 (m, 1H), 3.79 (s, 3H), 1.96–1.93 (m, 1H), 1.81–1.78 (m, 1H), 1.70–1.53 (m, 3H), 1.40–1.25 (m, 2H), 1.20–1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.2, 159.4, 145.9, 129.3 (×2), 128.7, 125.9, 124.4, 122.7, 117.4, 117.0, 114.3 (×2), 68.2, 61.1, 55.2, 48.6, 32.6, 32.5, 25.4, 24.6 (×2); MS (+ESI) *m/z* 433 (M+K$^+$, 100). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.10; H, 6.67; N, 7.12.

4.3.6. *N*-Cyclohexyl-2-(3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12f). A white crystalline solid and a 63:37 mixture of two diastereomers; mp 150–152 °C; IR (KBr) 1685, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.04–6.82 (m, 4H), 6.16 (s, 0.63H, major), 6.12 (s, 0.3H, minor), 5.98 (d, J=7.6 Hz, 1H), 4.75 (q, J=6.8 Hz, 0.37H, minor), 4.65 (q, J=6.8 Hz, 0.63H, major), 3.88–3.77 (m, 1H), 1.97–1.88 (m, 1H), 1.85–1.70 (m, 1H), 1.70–1.50 (m, 3H), 1.63 (d, J=7.2 Hz, 1.89H, major), 1.56 (d, J=6.8 Hz, 1.11H, minor), 1.42–1.23 (m, 2H), 1.20–0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.5, 166.8, 166.8, 145.3, 144.8, 134.1, 134.1, 128.8 (×2), 128.7 (×2), 128.7, 128.1, 128.1, 127.8 (×2), 127.6 (×2), 124.5, 124.3, 122.6, 122.5, 117.5, 117.5, 117.2, 117.0, 74.0, 74.0, 61.5, 61.2, 48.5, 48.5, 32.6, 32.6, 32.5, 32.5, 25.4, 25.4, 24.5 (×2), 24.5 (×2), 16.0, 16.0; MS (+ESI) *m/z* 401 (M+Na$^+$, 100). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.04; H, 6.95; N, 7.42.

4.3.7. *N*-Cyclohexyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(furan-2-yl)acetamide (12g). A white crystalline solid; mp 124–126 °C; IR (KBr) 1684, 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.16 (d, J=7.6 Hz, 1H), 7.00–6.90 (m, 3H), 6.61 (d, J=3.2 Hz, 1H), 6.47 (s, 1H), 6.36 (d, J=2.4 Hz, 1H), 6.09 (br d, J=7.6 Hz, 1H), 4.69 and 4.62 (ABq, J=15.2 Hz, 2H), 3.90–3.75 (m, 1H), 1.95–1.91 (m, 1H), 1.82–1.79 (m, 1H), 1.73–1.52 (m, 3H), 1.43–1.01 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.8, 147.1, 145.7, 142.8, 127.8, 124.4, 122.6, 117.0 (×2), 111.2, 110.8, 67.9, 54.0, 48.7, 32.6, 32.5, 25.3, 24.5, 24.5; MS (+ESI) *m/z* 377 (M+Na$^+$, 100). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.82; H, 6.43; N, 7.84.

4.3.8. *N*-Cyclohexyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(2-fluorophenyl)acetamide (12h). A white crystalline solid; mp 174–176 °C; IR (KBr) 1696, 1674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, J=7.4 Hz, 1H), 7.39–7.34 (m, 1H), 7.19–7.09 (m, 3H), 7.05–6.92 (m, 3H), 6.34 (s, 1H), 5.94 (br d, J=8.0 Hz, 1H), 4.73 and 4.65 (ABq, J=15.2 Hz, 2H), 3.92–3.80 (m, 1H), 1.99–1.96 (m, 1H), 1.88–1.82 (m, 1H), 1.74–1.55 (m, 3H), 1.44–1.25 (m, 2H), 1.22–1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.5, 160.7 (d, J_{C-F}= 246.9 Hz), 145.9, 130.5 (d, J_{F-C}=8.7 Hz), 129.4 (d, J_{F-C}= 2.5 Hz), 128.6, 124.6, 124.4 (d, J_{F-C}=3.3 Hz), 122.8, 121.7 (d, J_{F-C}=12.9 Hz), 117.1, 117.0, 115.8 (d, J_{F-C}= 18.7 Hz), 68.1, 56.2 (d, J_{F-C}=2.4 Hz), 48.7, 32.6, 32.5, 25.4, 24.6, 24.5; MS (+ESI) *m/z* 405 (M+Na$^+$, 100). Anal. Calcd for $C_{22}H_{23}FN_2O_3$: C, 69.09; H, 6.06; N, 7.33. Found: C, 69.16; H, 6.12; N, 7.47.

4.3.9. *N*-Benzyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12i). A white crystalline solid; mp 110–112 °C; IR (KBr) 1686, 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.15 (m, 10H), 7.02–6.94 (m, 3H), 6.82 (t, J=6.8 Hz, 1H), 6.58 (t, J=5.6 Hz, 1H), 6.18 (s, 1H), 4.65 and 4.56 (ABq, J=14.8 Hz, 2H), 4.44 (d, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.4, 145.9, 137.8, 133.8, 128.9, 128.9, 128.6, 128.5, 128.4, 128.3, 128.0 (×2), 127.5 (×2), 127.4, 124.5, 122.7, 117.5, 117.1, 68.1, 61.2, 43.8; MS (+ESI) *m/z* 395 (M+Na$^+$, 100). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.15; H, 5.52; N, 7.69.

4.3.10. *N*-Benzyl-2-(3,4-dihydro-2,6-dimethyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-phenylacetamide (12j). A white crystalline solid and a 56:44 mixture of two diastereomers; mp 142–144 °C; IR (KBr) 1689, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.24 (m, 10H), 7.00–6.83 (m, 3H), 6.63–6.60 (m, 1H), 6.27 (s, 0.56H, major), 6.22 (s, 0.44H, minor), 4.77–4.49 (m, 3H), 2.26 (s, 1.32H, minor), 2.22 (s, 1.68H, major), 1.67 (d, J=7.2 Hz, 1.68H, major), 1.62 (d, J=6.8 Hz, 1.32H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer: δ 168.6, 167.8, 143.1, 137.9, 134.0, 132.2, 128.8 (×2), 128.6 (×2), 128.5, 128.2, 127.9 (×2), 127.5 (×2), 127.3, 124.9, 117.6, 117.2, 74.0, 61.4, 43.7, 20.9, 16.0; ^{13}C NMR (100 MHz, $CDCl_3$) for the minor isomer: δ 168.5, 168.0, 142.7, 137.8, 134.0, 132.4, 128.9 (×2), 128.7, 128.6 (×2), 128.2, 127.7 (×2), 127.4 (×2), 127.3, 125.0, 117.6, 117.0, 74.0, 61.8, 43.7, 21.0, 15.9; MS (+ESI) *m/z* 423 (M+Na$^+$, 100). Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.95; H, 6.05; N, 6.95.

4.3.11. *N*-Benzyl-2-(3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(2-fluorophenyl)acetamide (12k). A white

crystalline solid; mp 133–135 °C; IR (KBr) 1692, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, J=7.6 Hz, 1H), 7.38–6.93 (m, 12H), 6.47 (t, J=2.0 Hz, 1H), 6.43 (s, 1H), 4.72 and 4.63 (ABq, J=15.2 Hz, 2H), 4.56 and 4.53 (ABqd, J=14.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.1, 160.7 (d, J_{F-C}= 246.9 Hz), 145.9, 137.6, 130.7 (d, J_{F-C}=8.6 Hz), 129.5 (d, J_{F-C}=3.0 Hz), 128.6 (×2), 128.5, 127.5 (×2), 127.4, 124.7, 124.6 (d, J_{F-C}=3.3 Hz), 122.8, 121.6 (d, J_{F-C}=13.2 Hz,), 117.2, 116.8, 115.9 (d, J_{F-C}=21.5 Hz), 68.1, 56.0 (d, J_{F-C}=2.5 Hz), 43.9; MS (+ESI) m/z 429 (M+K^+, 100). Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18. Found: C, 70.63; H, 4.92; N, 7.09.

4.3.12. *N*-Benzyl-2-(3,4-dihydro-7-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(2-bromophenyl)acetamide (12l). A white crystalline solid; mp169–170 °C (EtOAc–hexane); R_f=0.24 (20% EtOAc in hexane); IR (KBr) 3347, 1677, 1654, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J=8.0, 1.2 Hz, 1H), 7.55 (dd, J=8.0, 1.6 Hz, 1H), 7.33–7.23 (m, 6H), 7.20 (td, J=8.0, 1.6 Hz, 1H), 6.82 (s, 1H), 6.81 (d, J=8.0 Hz, 1H), 6.71–6.68 (m, 1H), 6.18 (t, J=4.8 Hz, 1H), 6.14 (s, 1H), 4.70 and 4.59 (ABq, J=15.2 Hz, 2H), 4.54 and 4.51 (ABqd, J=13.2, 4.8 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.1, 145.8, 137.7, 134.8, 133.6, 133.5, 130.4, 129.9, 128.6 (×2), 128.1, 127.6 (×2), 127.4, 126.5, 124.7, 123.3, 117.7, 116.4, 68.3, 62.9, 44.0, 20.7; MS (+ESI) m/z 489 (M+2+Na^+, 98), 487 (M+Na^+, 100). Anal. Calcd for $C_{24}H_{21}BrN_2O_3$: C, 61.95; H, 4.55; N, 6.02. Found: C, 61.98; H, 4.54; N, 6.09.

4.3.13. *N*-Benzyl-2-(3,4-dihydro-6-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(2-bromophenyl)acetamide (12m). A white crystalline solid; mp163–165 °C (CH_2Cl_2–hexane); R_f=0.24 (20% EtOAc in hexane); IR (KBr) 3298, 1685, 1670, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (td, J=8.0, 1.6 Hz, 2H), 7.33–7.23 (m, 6H), 7.20 (td, J=7.6, 1.6 Hz, 1H), 6.89 (d, J=8.0 Hz, 1H), 6.78 (d, J=8.0 Hz, 1H), 6.77 (s, 1H), 6.30 (br s, 1H), 6.16 (s, 1H), 4.67 and 4.56 (ABq, J=15.2 Hz, 2H), 4.55 and 4.49 (ABqd, J=14.8, 6.4 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.4, 143.8, 137.7, 133.6, 113.6, 132.5, 130.4, 130.2, 128.7, 128.6 (×2), 128.0, 127.6 (×2), 127.4, 125.1, 124.7, 117.3, 116.8, 68.4, 63.0, 43.9, 21.0; MS (+ESI) m/z 489 (M+2+Na^+,100), 487 (M+Na^+, 92). Anal. Calcd for $C_{24}H_{21}BrN_2O_3$: C, 61.95; H, 4.55; N, 6.02. Found: C, 61.54; H, 4.68; N, 5.94.

4.3.14. *N*-Benzyl-2-(3,4-dihydro-6-chloro-3-oxo-2*H*-1,4-benzoxazin-4-yl)-2-(2-bromophenyl)acetamide (12n). A white crystalline solid; mp 216–217 °C (CH_2Cl_2–hexane); R_f=0.22 (20% EtOAc in hexane); IR (KBr) 3312, 1691, 1672, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, J=7.2 Hz, 2H), 7.35–7.19 (m, 7H), 6.97 (s, 1H), 6.91 (s, 2H), 6.18 (t, J=5.6 Hz, 1H), 6.13 (s, 1H), 4.72 and 4.58 (ABq, J=15.2 Hz, 2H), 4.53 (d, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.9, 144.7, 137.4, 133.8, 132.8, 130.8, 130.3, 129.7, 128.7 (×2), 128.2, 127.7, 127.6 (×2), 127.5, 124.7, 124.4, 118.0, 117.3, 68.2, 62.8, 44.0; MS (+ESI) m/z 511 (M+4+Na^+,100), 509 (M+2+Na^+,100), 507 (M+Na^+, 77). Anal. Calcd for $C_{23}H_{18}BrClN_2O_3$: C, 56.87; H, 3.73; N, 5.77. Found: C, 56.88; H, 3.76; N, 5.73.

4.4. General procedure for microwave-assisted CuI-catalyzed intramolecular amidation of 12l–n

To a 10-mL pressurized process vial were added CuI (1.5×10^{-2} mmol, pre-washed by dry THF), the substrate **12l–n** (0.15 mmol), and $K_3PO_4\cdot3H_2O$ (0.30 mmol). The loaded vial was then sealed with a cap containing a silicon septum. The vial was evacuated and backfilled with nitrogen several times by using a needle through the septum. The degassed DMF (5 mL) was then added by syringe through the septum. The resultant mixture was heated in the microwave cavity at 150 °C for 35 min (for **12l**) or 50 min (for **12m** and **12n**). The reaction mixture was then filtrated through Celite with washing by EtOAc. The combined filtrate was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with EtOAc and petroleum ether (60–90 °C) to afford **13a–c**. The structures and yields of the products are given in Scheme 1.

4.4.1. *N*-Benzyl-3-(3,4-dihydro-7-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)oxindole (13a). A white crystalline solid and a 57:43 mixture of two atropisomers in $CDCl_3$; mp 113–114 °C (EtOAc–hexane); R_f=0.31 (20% EtOAc in hexane); IR (KBr) 1727, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major atropisomer: δ 7.41–6.87 (m, 9H), 6.81 (s, 1H), 6.75 (s, 1H), 6.27 (d, J=7.6 Hz, 1H), 5.73 (d, J=8.0 Hz, 1H), 5.11 and 4.79 (ABq, J=15.6 Hz, 2H), 4.79 and 4.69 (ABq, J=15.2 Hz, 2H), 2.13 (s, 3H); ^1H NMR (400 MHz, $CDCl_3$) for the minor atropisomer: δ 7.41–6.87 (m, 11H), 6.66 (d, J=7.6 Hz, 1H), 5.32 (s, 1H), 5.09 and 4.87 (ABq, J=15.6 Hz, 2H), 4.60 and 4.43 (ABq, J= 15.2 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major atropisomer: δ 171.9, 166.0, 145.4, 142.2, 135.3, 134.4, 129.4, 128.8 (×3), 128.1 (×2), 127.5, 124.1, 123.6, 123.1, 122.7, 117.9, 115.2, 109.9, 67.7, 53.2, 44.4, 20.6; ^{13}C NMR (100 MHz, $CDCl_3$) for the minor atropisomer: δ 171.7, 164.0, 145.4, 143.4, 135.4, 134.8, 129.4, 128.7 (×3), 128.0, 127.2 (×2), 124.3, 123.7, 123.3, 123.0, 118.1, 114.2, 109.6, 67.9, 56.2, 44.2, 20.7; MS (−ESI) m/z 383 (M−H^+, 100). Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.89; H, 5.20; N, 7.33.

4.4.2. *N*-Benzyl-3-(3,4-dihydro-6-methyl-3-oxo-2*H*-1,4-benzoxazin-4-yl)oxindole (13b). A white crystalline solid and a 52:48 mixture of two atropisomers in DMSO-d_6; mp 151–152 °C (EtOAc–hexane); R_f=0.30 (20% EtOAc in hexane); IR (KBr) 1730, 1685 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) for the major atropisomer: δ 7.47–6.86 (m, 11H), 6.73 (d, J=8.0 Hz, 1H), 5.43 (s, 1H), 5.15 and 4.95 (ABq, J=16.0 Hz, 2H), 4.64 and 4.48 (ABq, J=15.2 Hz, 2H), 2.39 (s, 3H); ^1H NMR (400 MHz, DMSO-d_6) for the minor atropisomer: δ 7.47–6.86 (m, 11H), 6.68 (d, J=8.4 Hz, 1H), 5.75 (s, 1H), 5.22 and 4.82 (ABq, J= 15.6 Hz, 2H), 4.82 and 4.76 (ABq, J=15.2 Hz, 2H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) for the major atropisomer: δ 172.1, 164.6, 143.7, 143.7, 135.7, 132.5, 130.0, 129.6, 129.0 (×2), 127.8, 127.5 (×2), 125.2, 124.4, 123.5, 123.0, 117.2, 115.3, 109.9, 68.2, 56.5, 44.5, 21.4; ^{13}C NMR (125 MHz, $CDCl_3$) for the minor atropisomer: δ 172.0, 166.6, 143.8, 142.5, 135.7, 133.3, 129.7, 129.2 (×2), 128.2, 128.2 (×2), 126.8, 124.9, 124.3, 123.7, 123.2, 117.5, 116.2, 110.0, 68.1, 53.5, 44.7, 21.0; MS (+ESI) m/z

407 ($M+Na^+$, 100), 791 ($2M+Na^+$, 77). Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.79; H, 5.24; N, 7.27.

4.4.3. *N*-Benzyl-3-(3,4-dihydro-6-chloro-3-oxo-2*H*-1,4-benzoxazin-4-yl)oxindole (13c). A white crystalline solid and a 51:49 mixture of two atropisomers in $CDCl_3$; mp 193–195 °C (EtOAc–hexane); R_f=0.31 (20% EtOAc in hexane); IR (KBr) 1731, 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major atropisomer: δ 7.45–6.88 (m, 11H), 6.73 (d, J=8.4 Hz, 1H), 6.02 (d, J=2.0 Hz, 1H), 5.13 and 4.91 (ABq, J=16.0 Hz, 2H), 4.65 and 4.49 (ABq, J=15.2 Hz, 2H); ^1H NMR (400 MHz, $CDCl_3$) for the minor atropisomer: δ 7.45–6.88 (m, 12H), 5.33 (s, 1H), 5.19 and 4.86 (ABq, J=15.6 Hz, 2H), 4.84 and 4.78 (ABq, J=15.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major atropisomer: δ 171.4, 165.8, 144.3, 142.2, 135.1, 131.1, 129.9, 129.2 (×2), 127.9, 127.6, 127.5 (×2), 124.1, 123.6, 123.5, 122.8, 118.4, 115.5, 110.3, 67.6, 53.3, 44.6; ^{13}C NMR (100 MHz, $CDCl_3$) for the minor atropisomer: δ 171.4, 163.8, 144.2, 143.3, 135.3, 129.6, 128.8 (×2), 128.3, 127.9, 127.6, 127.2 (×2), 124.3, 124.0, 122.9, 122.7, 118.6, 114.8, 109.8, 67.8, 56.4, 44.2; MS (+ESI) m/z 831.0 ($2M+Na^+$, 45); 429 ($M+2+Na^+$, 33), 427 ($M+Na^+$, 100). Anal. Calcd for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.14; H, 4.19; N, 6.75.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2006.05.001.

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